Application No.: 09/251570 Group Art Unit: 1644

## REMARKS

Claim Amendments

Claims 1-21 are currently pending. Claim 19 has been canceled without prejudice to expedite prosecution and to reduce the number of issues for appeal. Claims 1 and 2 have been amended to incorporate the subject matter of canceled claim 19.

Claims 1 and 2 have been further amended to specify that the first and second agents are different. Support for the amendment of claims 1 and 2 can be found throughout the specification as originally filed. In addition, in view of the fact that the claims as originally filed included dependent claims specifying different first and second binding agents, the amendments herein to claims 1 and 2 should not require an additional search.

The foregoing amendments should in no way be construed as an acquiescence to any of the Examiner's rejections, and have been made solely to expedite examination of the present application and to place the pending claims in better condition for appeal. No new issues have been raised and no additional search should be required. Accordingly, Applicant respectfully requests that the foregoing claim amendments be entered. Applicant reserves the right to pursue the claims as originally filed in this or a separate application(s). No new matter has been added.

Applicant Respectfully Traverses the Finality of the Present Office Action

The first Office Action in the present application was mailed from the Patent Office on April 9, 2002. Applicant's response to this first Office Action was submitted on October 9, 2002. The second (*i.e.*, the present) and final Office Action was mailed from the Patent Office on February 25, 2003. In this second and final Office Action, the Examiner has introduced several new grounds of rejection which were not necessitated by the amendment of the application in the response dated October 9, 2002 and, thus, which could have been raised in the initial Office Action. Therefore, Applicant respectfully submits that the finality of the Office Action mailed on February 25, 2003 is improper and requests that the present Amendment be entered and considered as an amendment prior to final rejection.

In the final Office Action, claims 1-8, 10-13, 15, 16, 18, and 19 are rejected under 35 U.S.C. §102(a) or §102(e) as being anticipated by Fanger *et al.* (U.S. Patent No. 5,635,600). Specifically, the Examiner states that:

> Fanger *et al.* teach a method of reducing the number of macrophages by targeting human macrophages for treating diseases including cancer, allergies, infectious and autoimmune diseases by local administration of a bifunctional antibody (*i.e.*, a compound comprising a first agent which binds to an Fc receptor derived from monoclonal antibody 22, 32 or 197, and a second agent which kills or reduces the activity of the macrophages . . . Therefore, the referenced teachings anticipate the claimed invention.

Applicant's amendment dated October 9, 2002 did not necessitate this rejection by the Examiner. The method claims rejected by the Examiner, *i.e.*, methods of selectively reducing the number or activity of macrophages using a macrophage-binding compound comprising a first agent which binds to an Fc receptor and a second agent which kills or reduces the activity of the macrophages (*e.g.*, an anti-Fc receptor antibody conjugated to a toxin), were present in Applicant's claims as originally filed. However, no rejection relating to their novelty in view of Fanger *et al.* was made in the first Office Action dated April 9, 2002.

In the final Office Action, claims 1-10, 18, 20, and 21 are also rejected under 35 U.S.C. §103(a) as being unpatentable over Fanger *et al.*, Graziano *et al.*, and Erickson *et al.*, in view of Uhr *et al.*, Ghetie *et al.*, Rybak *et al.*, Pastan *et al.*, and Bjerke *et al.* Specifically, the Examiner states that:

> it would have been obvious to one of skill in the art at the time the invention was made to have combined the immunotoxin technology taught by Vitetta [Ghetie?], Rybak and Pastan which comprises an antibody or antibody fragment thereof that binds to FcγRI as taught by Erickson, Graziano and Fanger linked to a toxin as taught by Vitetta, Rybak and Pastan because said immunotoxin will bind to an FcγRI receptor and kill or reduce the activity of FcγRI bearing macrophages. Furthermore, it would have been obvious to one of skill in the art at the time the invention was made to have used said immunotoxin in treating or preventing a disease characterized by aberrant activity or number of macrophages . . . as taught by Bjerke and Fanger, respectively . . .

Applicant's amendment dated October 9, 2002 did not necessitate this rejection by the Examiner. The method claims rejected by the Examiner, *i.e.*, methods of selectively reducing the number or activity of macrophages using a macrophage-binding compound comprising a first agent which binds to an Fc receptor and a second agent which kills or reduces the activity of the macrophages (*e.g.*, an anti-Fc receptor antibody conjugated to a toxin), were present in Applicant's claims as originally filed. However, no rejection relating to their patentability in view of the cited references was made in the first Office Action dated April 9, 2002.

In the final Office Action, claims 1 and 13-17 are also rejected under 35 U.S.C. §103(a) as being unpatentable over Fanger *et al.*, Graziano *et al.*, and Erickson *et al.*, in view of McGrath *et al.*, Estis *et al.*, Rodwell *et al.*, Lifson *et al.*, and Bagshawe *et al.*. Specifically, the Examiner states that:

> it would have been obvious to one of skill in the art at the time the invention was made to have combined the macrophage binding monoclonal antibody compounds taught by Erickson, Graziano and Fanger within a liposome in the claimed method because said compounds bind macrophages as taught by Erickson, Graziano and Fanger . . . and because Liffson *et al.* teach that a protein may be administered in a liposome-encapsulated form, and antibodies are proteins and because Rodwell *et al.* teaches that liposomes are readily phagocytosed by macrophages. Furthermore, it would have been obvious . . . to have used single chain antibody, or fragment thereof of the FcγRI binding monoclonal antibodies taught by Erickson, Graziano and Fanger since Bagshawe teaches the advantage of using antibody fragments including improved pharmacological properties. Furthermore, it would have been obvious . . . to have combined the cytotoxic agent CL2MDP in a liposome . . . because Estis teach that liposomes can carry CL2MDP and because McGrath teaches a method that features a liposome preparation containing within the liposome macrophage-specific cytotoxin . . .

Applicant's amendment dated October 9, 2002 did not necessitate this rejection by the Examiner. The method claims rejected by the Examiner, *i.e.*, methods of selectively reducing the number or activity of macrophages using liposome-encapsulated agents or using CL2MDP or using single chain antibodies, were present in Applicant's claims as originally filed. In fact, such claims are currently pending in their original unamended form. However, no rejection relating to their patentability in view of the cited references was made in the first Office Action dated April 9, 2002.

Accordingly, as discussed above, Applicant respectfully submits that, contrary to the assertion at page 9 of the final Office Action, Applicant's amendment did not necessitate all of the new grounds of rejection presented in the second and final Office Action dated February 25, 2003. Therefore, Applicant respectfully requests that the finality of the second Office Action be removed.

***Rejection of Claims 1-6 Under 35 U.S.C. § 102(a)***

The Examiner maintains the rejection of claims 1-6 under 35 U.S.C. §102(a) as being anticipated by Curnow, R. (*Cancer Immunol. Immunother.* 45:210-215 (1997)), as evidenced by Graziano *et al.* (*J. Immunol.* 155:4996-5002 (1995)). In particular, the Examiner alleges that Curnow teaches that "down modulating CD64 by CD64 specific antibodies reduces the activity

of CD64 bearing cells such as macrophages" and that the agent disclosed by Graziano has the function of the claimed invention.

Applicant respectfully traverses this rejection. However, to expedite prosecution, independent claims 1 and 2 have been amended to specify that the first and second agents are different. The cited reference fails to teach or suggest the claimed methods which require two separate and distinct agents, *i.e.*, a first agent which binds to an Fc receptor and a second agent which kills or reduces the activity of the macrophage.

***Rejection of Claims 1-6 and 18 Under 35 U.S.C. § 102(b)***

The Examiner maintains the rejection of claims 1-6 and 18 under 35 U.S.C. §102(b) as being anticipated by Ericson *et al.* (*British Journal of Haematology*, 92:718-724 (1996)). The Examiner states that Ericson *et al.* teach a monoclonal antibody that can bind and down modulate FcγRI receptor on circulating monocytes, *e.g.*, in ITP patients, and thus, which has the function of the agents recited in the present claims.

Applicant respectfully traverses this rejection. However, to expedite prosecution, independent claims 1 and 2 have been amended to specify that the first and second agents are different. The cited reference fails to teach or suggest the claimed methods which require two separate and distinct agents, a first agent which binds to an Fc receptor and a second agent which kills or reduces the activity of the macrophages.

Claims 1-6 and 18 have also been amended to incorporate the subject matter of claim 19, to which this rejection does not apply. Accordingly, this rejection is now moot.

***Rejection of Claims 1, 2, 8-12, and 21 Under 35 U.S.C. § 103(a)***

The Examiner maintains the rejection of claims 1-2, 8-12, and 21 under 35 U.S.C. §103(a) as being unpatentable over Curnow, R.T. (cited *supra*), Graziano *et al.* (cited *supra*), Ericson *et al.* (cited *supra*), Uhr *et al.* (USPN 5,686,072), Ghetie *et al.* (USPN 5,578,706), Rybak *et al.* (USPN 5,840,840), Pastan (USPN 5,489,525), and Bjerke *et al.* (ACTA Derm. Venereol. (Stockh) Suppl. 186:141-142 (1994)). In particular, the Examiner states that the cited references are not limited to monocytes but also include macrophages. The Examiner also states that

administration of the mab taught by the cited references into the circulatory system wold contact macrophages in a tissue.

Applicant respectfully traverses this rejection. However, to expedite prosecution, independent claims 1 and 2 have been amended to incorporate the subject matter of claim 19, to which this rejection does not apply. Accordingly, this rejection is now moot. None of the cited references, either alone or in combination, teach or suggest the claimed methods which selectively reduce the number or activity of macrophages within a selected area of the subject, by contacting the area of tissue, either topically, intradermally or subcutaneously, with a macrophage-binding compound which comprises a first agent that binds to an Fc receptor at a site that is distinct the endogenous immunoglobulin binding site and a second different agent which kills or reduces the activity of the macrophages.

***Rejection of Claims 1-8, 10-13, 15, 16, 18, and 19 Under 35 U.S.C. §102(a) or 102(e)***

Claims 1-8, 10-13, 15, 16, 18, and 19 are rejected under 35 U.S.C. §102(a) or §102(e) as being anticipated by Fanger *et al.* (U.S. Patent No. 5,635,600). Specifically, the Examiner states that:

> Fanger *et al.* teach a method of reducing the number of macrophages by targeting human macrophages for treating diseases including cancer, allergies, infectious and autoimmune diseases by local administration of a bifunctional antibody (*i.e.*, a compound comprising a first agent which binds to an Fc receptor derived from monoclonal antibody 22, 32 or 197, and a second agent which kills or reduces the activity of the macrophages . . . Therefore, the referenced teachings anticipate the claimed invention.

Applicant respectfully traverses this rejection. The claims, as amended, are drawn to a method of selectively reducing the number or activity of macrophages, and a method of treating a disease in a subject characterized by aberrant activity or numbers of macrophages, within a selected area of the subject, by contacting the area of tissue with a macrophage-binding compound which comprises a first agent that binds to an Fc receptor at a site that is distinct the endogenous immunoglobulin binding site and a second different agent which kills or reduces the activity of the macrophages, wherein the macrophage-binding compound is administered topically, intradermally or subcutaneously in a pharmaceutically acceptable carrier. The cited reference fails to teach or suggest the claimed invention.

In particular, Fanger *et al.* describe bispecific antibodies which bind to human effector cells, *e.g.*, macrophages, and a target antigen so that "the targeted effector cells [*i.e.*,

macrophages] can be used to kill target cells by cell mediated antibody dependent cytolysis" (see, Abstract). The bispecific antibodies include a portion that binds to an Fc receptor on an effector cell and a portion that binds to a target cell. The bispecific antibodies taught by Fanger *et al.* do not reduce the number or activity of macrophages to which they bind, but instead function to reduce the number or activity of the target cell to which they bind. In fact, Fanger *et al.* teach away from reducing the number or activity of macrophages since these effector cells are necessary to kill target cells. That is, depleting the number or activity of the macrophages would deplete the effectiveness of the bifunctional antibodies described in Fanger *et al.* As explained in Fanger *et al.*, the bifunctional antibodies are "used to produce target-specific effector cells, *i.e.*, effector cells which are capable of recognizing and binding to a target cell and exerting their effector function . . . effector cells, such as macrophages, targeted in this way can be employed to bring about antibody dependent cell-mediated killing of target cells" (col. 5, lines 17-28).

Therefore, based on at least the foregoing, the claims are novel and inventive in view of Fanger *et al.*

***Rejection of Claims 1-10, 18, 20, and 21 Under 35 U.S.C. §103(a)***

Claims 1-10, 18, 20, and 21 are rejected under 35 U.S.C. §103(a) as being unpatentable over Fanger *et al.* (U.S. Patent No. 5,635,600), Graziano *et al.*, and Erickson *et al.*, in view of Uhr *et al.*, Ghetie *et al.*, Rybak *et al.*, Pastan *et al.*, and Bjerke *et al.* Specifically, the Examiner states that:

> it would have been obvious to one of skill in the art at the time the invention was made to have combined the immunotoxin technology taught by Vitetta [Applicant assumes the Examiner is referring to Ghetie here], Rybak and Pastan which comprises an antibody or antibody fragment thereof that binds to FcγRI as taught by Erickson, Graziano and Fanger linked to a toxin as taught by Vitetta [Ghetie], Rybak and Pastan because said immunotoxin will bind to an FcγRI receptor and kill or reduce the activity of FcγRI bearing macrophages. Furthermore, it would have been obvious to one of skill in the art at the time the invention was made to have used said immunotoxin in treating or preventing a disease characterized by aberrant activity or number of macrophages . . . as taught by Bjerke and Fanger, respectively . . .

Applicant respectfully traverses this rejection. None of the cited references, either alone or in combination, teach or suggest the claimed methods which selectively reduce the number or activity of macrophages within a selected area of the subject, by contacting the area of tissue with a macrophage-binding compound which comprises a first agent that binds to an Fc receptor

at a site that is distinct the endogenous immunoglobulin binding site and a second different agent which kills or reduces the activity of the macrophages.

However, to expedite prosecution, independent claims 1 and 2 have been amended to incorporate the subject matter of claim 19 to which this rejection does not apply. Accordingly, this rejection is now moot.

***Rejection of Claims 1 and 13-17 Under 35 U.S.C. §103(a)***

Claims 1 and 13-17 are rejected under 35 U.S.C. §103(a) as being unpatentable over Fanger *et al.*, Graziano *et al.*, and Erickson *et al.*, in view of McGrath *et al.*, Estis *et al.*, Rodwell *et al.*, Lifson *et al.*, and Bagshawe *et al.*. Specifically, the Examiner states that:

> it would have been obvious to one of skill in the art at the time the invention was made to have combined the macrophage binding monoclonal antibody compounds taught by Erickson, Graziano and Fanger within a liposome in the claimed method because said compounds bind macrophages as taught by Erickson, Graziano and Fanger . . . and because Liffson *et al.* teach that a protein may be administered in a liposome-encapsulated form, and antibodies are proteins and because Rodwell *et al.* teaches that liposomes are readily phagocytosed by macrophages. Furthermore, it would have been obvious . . . to have used single chain antibody, or fragment thereof of the FcγRI binding monoclonal antibodies taught by Erickson, Graziano and Fanger since Bagshawe teaches the advantage of using antibody fragments including improved pharmacological properties. Furthermore, it would have been obvious . . . to have combined the cytotoxic agent CL2MDP in a liposome . . . because Estis teach that liposomes can carry CL2MDP and because McGrath teaches a method that features a liposome preparation containing within the liposome macrophage-specific cytotoxin . . .

Applicant respectfully traverses this rejection. None of the cited references, either alone or in combination, teach or suggest the claimed methods which selectively reduce the number or activity of macrophages within a selected area of the subject, by contacting the area of tissue with a macrophage-binding compound which comprises a first agent that binds to an Fc receptor at a site that is distinct the endogenous immunoglobulin binding site and a second different agent which kills or reduces the activity of the macrophages.

However, to expedite prosecution, independent claim 1 has been amended t incorporate the subject matter of claim 19 to which this rejection does not apply. Accordingly, this rejection is now moot.

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## CONCLUSION

In view of the foregoing, entry of the amendments and remarks herein, reconsideration and withdrawal of all rejections, and allowance of the instant application with all pending claims are respectfully solicited. If a telephone conversation with Applicant's attorney would help expedite the prosecution of the above-identified application, the Examiner is urged to call Applicant's attorney at (617) 227-7400.

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Respectfully submitted,

By _____

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